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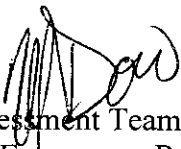
MEMORANDUM

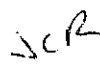
DATE: 08 DECEMBER 2009

SUBJECT: DIFENOCONAZOLE – Human Exposure/Risk Assessment for the
 Proposed New Use of Difenconazole on Golf Course Turf Grass.

PC Code: 128847
 MRID No.: None
 Petition No.: None
 Assessment Type: ORE
 TXR No.: None

DP Barcode: D371382
 EPA Reg. No. 100-1313
 Regulatory Action: Section 3
 Reregistration Case No.: None
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INTRODUCTION

Under provisions in Section 3 of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), as amended, the Syngenta Crop Protection, Inc., has requested an amendment to a currently registered product, Quadris Top™ (EPA Reg. No. 100-1313). The requested amendment is to add the use of the active ingredient difenoconazole to golf course turf. No residential turf uses are being requested.

The risk assessment techniques used in this document are those that have been developed and refined by the HED/Office of Pesticide Programs' Science Policy Council for Exposure (ExpoSAC). RD herein utilizes those techniques.

USE PATTERN SUMMARY

The use pattern summary is taken from draft labeling for Quadris Top™ Fungicide label (EPA Reg. No. 100-1313). Quadris is formulated as a suspension concentrate liquid which contains 1.05 lb (11.4 %) active ingredient (ai) difenoconazole per gallon. Quadris also contains the fungicide ai azoxystrobin. Azoxystrobin is currently registered for use on golf course turf therefore an assessment of azoxystrobin is not necessary.

The target pests are various species of turf disease organisms in the genera: *Agrocybe*, *Bipolaris*, *Bovistia*, *Colletotrichum*, *Drechslera*, *Erysiphe*, *Gaeumannomyces*, *Laetisaria*, *Limonomyces*, *Lycoperdon*, *Magnaporthe*, *Microdochium*, *Ophiosphaerella*, *Puccinia*, *Pyricularia*, *Rhizoctonia*, *Sclerotinia*, and *Waitea*. Depending upon the pest species, the rate of application varies from 11.0-30.5 fl oz formulation per acre (0.09-0.25 lb ai/A). There is a maximum of 0.52 lb ai difenoconazole that may be applied per acre per year. It should be applied in 30 – 450 gallons of spray per acre by ground equipment. It may NOT be applied to golf course turf by aircraft or through any type of irrigation system. Re-application intervals vary from 14-28 days according to target pest species.. No more than two sequential applications may be made to control gray leaf spot. For all other diseases, when gray leaf spot is not present, no more than three sequential applications should be made.

The product label directs applicators and other occupational pesticide handlers to wear personal protective equipment (PPE) which consists of: long-sleeved shirt, long pants, shoes plus socks and chemical resistant gloves made of any waterproof material such as polyvinyl chloride, nitrile rubber or butyl rubber.

See Table 1.0 for a summary of the proposed new use pattern.

Table 1.0 Summary of Proposed Use Pattern for Applying Difenoconazole to Golf Course Turf grass	
Formulation	Quadris Top Fungicide; Reg. No. 100-1313; 1.05 lb ai/gal difenoconazole (11.4 %); also contains 1.67 lb ai/gal azoxystrobin; soluble concentrate liquid.
Pest	Numerous species of pathogenic turf grass organisms
Method of Applic.	ground-boom, low pressure hand-gun, backpack sprayer
Applic. Rate	0.09-0.25 lb ai/A
Max. No. Applications	2 per year at the high rate; 6 per year at the low rate
Max. Am't/Yr	0.52 lb ai/A/yr
Applic. Interval	14-28 days
Restricted Entry Interval	12 hours for crops covered by the worker protection standard (WPS)
Manufacturer	Syngenta Crop Protection, Inc.

OCCUPATIONAL PESTICIDE HANDLER EXPOSURE

Based upon the proposed use pattern, ARIA/RD believes the most highly exposed occupational pesticide handlers will be:

- 1) mixer/loader using open pour loading of liquid formulation
- 2) applicator using open cab, ground-boom sprayer,
- 3) mixer/loader/applicator using low pressure hand-gun sprayer
- 4) mixer/loader/applicator using backpack sprayer.

Private (i.e., grower) applicators may perform all functions, that is, mix, load and apply the material. The ExpoSAC standard procedure directs that although the same individual may perform all those tasks, in many cases they shall be assessed separately. By separating the job functions, HED/RD determine the most appropriate levels of personal protective equipment (PPE) for each aspect of the job without requiring an applicator to wear unnecessary PPE that might be required for a mixer/loader (e.g., chemical resistant gloves may only be necessary during the pouring of a liquid formulation).

These exposure scenarios are outlined in the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (August 1998). Most exposure scenarios for hand-held equipment (such as hand wands, backpack sprayers, and push-type granular spreaders) are assessed as a combined job function. With these types of hand held operations, all handling activities are assumed to be conducted by the same individual.

No chemical specific data were available with which to assess potential exposure to pesticide handlers. The estimates of exposure to pesticide handlers are based upon surrogate study data available in the PHED (v. 1.1, 1998). The product label directs applicators and other handlers to wear long-sleeved shirt, long pants, shoes plus socks and water-proof gloves.

The toxicological factors used in this assessment are taken from the Agency's most recent risk assessment regarding difenoconazole: Memorandum, 16 OCT 2009, Y. Donovan et al., DP Code 367382, Petition No. 8F7482, "**Difenoconazole** FQPA Human Health Risk Assessment for the Section 3 Registration of Difenoconazole new Uses on Bulb Vegetables, Brassica Leafy Vegetables, Cucurbit Vegetables, Citrus Fruits, Grapes, Pistachios, and Tree Nuts."

As pertains to the assessment herein, the Agency identified short- and intermediate-term dermal toxicological endpoints. The oral No Observable Adverse Effect Level (NOAEL) is 1.25 mg/kg bw/day. The NOAEL was identified from a rat feeding study. It was based on the observed reduction in body weight gain of F₀ females prior to mating, gestation and lactation. The Agency identified a dermal absorption factor of 15.3 % to extrapolate dermal exposure from an oral endpoint. The Level of Concern (LOC) for occupational exposures is for Margins of Exposure (MOE) < 100.

The Agency also identified inhalation toxicological endpoints. The inhalation endpoints were identified from the same oral study in the rat and cite the same toxic effects and the

same NOAEL as for the dermal route of exposure. The LOC is also for MOEs < 100. The Agency assumes 100 % absorption via the inhalation route of exposure.

Difenoconazole is classified as a Group C, possible human carcinogen with a non-linear (MOE) approach for human risk characterization (CPRC Document, 7/27/94, Memo, P.V. Shah dated March 3, 2007, HED Doc. No. 0054532). Therefore, a cancer risk assessment is not necessary since chronic exposure is not expected as a result of the proposed use pattern. See the ATTACHMENT for a summary of toxicological endpoints used for risk assessment. See Table 2.0 for a summary of exposures and risks to occupational pesticide handlers.

Table 2.0 Summary of Exposure & Risk to Occupational Handlers From Applying Difenoconazole to Golf Course Turf				
Unit Exposure¹ mg ai/lb handled	Applic. Rate² lb ai/unit	Units Treated³	Avg. Daily Exposure⁴ mg ai/kg bw/day	MOE⁵
Mixer/Loader - Liquid - Open Pour				
Dermal: SLNoGlove 2.9 SLWithGlove 0.023 Inhal. 0.0012	0.25 lb ai/A	40 A/day	Dermal: SLNoGlove 0.0634 SLWithGlove 0.000503 Inhal. 0.00017	No Glove 20 With Glove 1860
Applicator - Ground-boom - Open-cab				
Dermal: SLNoGlove 0.014 SLWithGlove 0.014 Inhal. 0.00074	0.25 lb ai/A	40 A/day	Dermal: SLNoGlove 0.00031 SLWithGlove 0.00031 Inhal. 0.000106	No Glove 3000 With Glove 3000
Mixer/Loader/Applicator Low Pressure Handgun (Liquid open pour)*				
Dermal: SLWithGlove 0.45 Inhal. 0.0015	0.25 lb ai/A	5 A/day	Dermal: SLWithGlove 0.00123 Inhal. 0.0000268	With Glove 1,000
Mixer/Loader/Applicator Backpack (Liquid open pour)				
Dermal: SLNoGlove no data SLWithGlove 2.5 Inhal. 0.03	0.25 lb ai/A	40 gal/day (0.333 lb ai/day)*	Dermal: SLNoGlove no data SLWithGlove 0.00182 Inhal. 0.000143	With Glove 640

1. Unit Exposures are taken from "PHED SURROGATE EXPOSURE GUIDE", Estimates of Worker Exposure from The Pesticide Handler Exposure Database Version 1.1, August 1998. Dermal = Single Layer Work Clothing **No Gloves**; Single Layer Work Clothing **With Gloves**; Inhal. = Inhalation. Units = mg a.i./pound of active ingredient handled. * Unit exposure for mixer/loader/applicator low pressure hand-gun taken from Outdoor Residential Exposure TaskForce (ORETF) study; MRID 449722-01. Syngenta is a member of the ORETF.

2. Applic. Rate. = Taken from draft Quadris Top labeling for use on golf course turf

3. Units Treated are taken from "Standard Values for Daily Acres Treated in Agriculture"; ExpoSAC SOP No. 9.1. Revised 25 September 2001;

4. Average Daily Dose = Unit Exposure * (Applic. Rate * Units Treated) or (amount ai/day) * 15.3 % dermal absorption ÷ 70 kg Body Weight

5. MOE = Margin of Exposure = NOAEL ÷ ADD. Short- and intermediate-term dermal and inhalation NOAEL = 1.25 mg/kg bw/day. Dermal and inhalation average daily exposures are summed prior to dividing into NOAEL since the endpoints are the same, cite the same effects and are identified from the same study.

* The label suggests applying spray at rates of 30-450 gallons of spray per acre. The highest concentration of active ingredient occurs with the use of 30 gallons per acre. (0.25 lb ai/A ÷ 30 gal spray/A = 0.00833 lb ai/gal spray; 0.0083 lb ai/gal spray * 40 gal spray/day = 0.333 lb ai/day)

A MOE of 100 is adequate to protect occupational pesticide handlers from exposures to difenoconazole. Provided mixer/loaders wear protective gloves as directed by the label, the MOEs are > 100 thus do not exceed the Agency's level of concern.

POST-APPLICATION EXPOSURE TO AGRICULTURAL WORKERS

It is possible for golf course maintenance workers as well as adult and "child" golfers to experience post-application exposure to pesticide residues during the course of typical activities involved with golfing or with golf course maintenance. HED in conjunction with the Agricultural Re-entry Task Force (ARTF) has identified a number of post-application activities that may occur and which may result in post-application exposures to pesticide residues. HED has also identified transfer coefficients (TC) (cm²/hr) relative to the various activities which express the amount of foliar contact over time, during each of the activities identified. For workers performing typical golf course maintenance activities, the TC is 3,400 cm²/hr. The TC is taken from an Agricultural Re-entry Task Force (ARTF) study (MRID 45530101). The study data may only be used by members of the ARTF. Syngenta is a member of the ARTF.

The TC for adult and child golfers is taken from a draft Standard Operating Procedure: "Golfer Exposure Assessment for Adults and Children". The TC is 500 cm²/hr.

Lacking compound specific dislodgeable foliar residue (DFR) data, HED assumes 5 % of the application rate is available as turf transferable residue on day zero after application.

The following convention may be used to estimate post-application exposure to golf course maintenance workers.

$$\text{Average Daily Dose (ADD) (mg a.i./kg bw/day)} = \text{TTR } \mu\text{g/cm}^2 * \text{TC cm}^2/\text{hr} * \text{hr/day} * 0.001 \text{ mg}/\mu\text{g} * 1/70 \text{ kg bw}$$

and where:

$$\text{Surrogate Turf Transferrable Residue (TTR)} = \text{application rate} * 5\% \text{ available as dislodgeable residue} * 4.54 \times 10^8 \mu\text{g/lb} * 2.47 \times 10^{-8} \text{ A/cm}^2.$$

$$0.25 \text{ lb a.i./A} * 0.05 * 4.54 \times 10^8 \mu\text{g/lb} * 2.47 \times 10^{-8} \text{ A/cm}^2 = 0.14 \mu\text{g/cm}^2, \text{ therefore,}$$

$$0.14 \mu\text{g/cm}^2 * 3,400 \text{ cm}^2/\text{hr} * 8 \text{ hr/day} * 0.001 \text{ mg}/\mu\text{g} * 0.153 (\% \text{ dermal absorption}) \div 70 \text{ kg bw} = 0.00833 \text{ mg/kg bw/day}.$$

$$\text{MOE} = \text{NOAEL} \div \text{ADD then } 1.25 \text{ mg/kg bw/day} \div 0.0083 \text{ mg/kg bw/day} = 150.$$

Since the MOE is > 100, the proposed use does not exceed the Agency's level of concern.

Adult and Adolescent Golfer Post-Application Dermal Exposure may be estimated using the convention stated in Science Advisory Council for Exposure draft SOP regarding

“Golfer Exposure Assessment For Adults and Children” (24 August 2000). The draft policy states that adult and adolescent golfer dermal post-application exposure may be calculated as $DE_{(t)}$ (mg a.i./kg bw/day) = $(TTR_{(t)} (\mu\text{g}/\text{cm}^2)) * TC (\text{cm}^2/\text{hr}) * \text{hr}/\text{day} \div (CF (1000 \mu\text{g}/\text{mg})) * BW$ (body weight (kg)) Where:

$DE_{(t)}$ = dermal exposure at time (t) attributable to golfing on previously treated turf (mg a.i./kg bw/day).

$TTR_{(t)}$ = turf transferable residue at time t ($\mu\text{g}/\text{cm}^2$)

TC = Transfer Coefficient ($500 \text{ cm}^2/\text{hr}$)

hr = exposure period (4 hours)

DA = dermal absorption (15.3 %)

CF = conversion factor to change μg to mg.

BW = body weight (kg) (70 kg for adult; adjusted (multiplied) by a factor of 1.7 for child golfers)). A BW of 60 kg is utilized if the toxicological endpoint is derived from a developmental study and there are fetal effects.

and where $TTR_t = AR * F * CF2 * CF3$

AR = application rate (lb ai/acre); 0.001 lb ai/acre

F = fraction of ai available on turf/grass (unitless); 5%

CF2 = weight unit conversion factor to convert the lbs ai in the application rate to use for the DFR or GR value ($4.54\text{E}+8 \mu\text{g}/\text{lb}$)

CF3 = area unit conversion factor to convert the surface area units (acre) in the application rate to cm^2 for the TTR or GR value ($2.47\text{E}-8 \text{ acre}/\text{cm}^2$)

Therefore, $0.25 \text{ lb ai/A} * 0.05 (\%) * 4.54^8 \mu\text{g}/\text{lb} * 2.47^{-8} \text{ A}/\text{cm}^2 = 0.14 \mu\text{g}/\text{cm}^2$

$DE = 0.14 \mu\text{g}/\text{cm}^2 * 500 \text{ cm}^2/\text{hr} * 4 \text{ hr}/\text{day} * 0.001 \mu\text{g}/\text{mg} * 0.153 (\% \text{ dermal absorption}) \div 70 \text{ kg bw} = 0.000612 \text{ mg a.i.}/\text{kg bw}/\text{day}$.

MOE for adult golfer is $1.25 \text{ mg a.i.}/\text{kg bw}/\text{day} \div 0.000612 \text{ mg a.i.}/\text{kg bw}/\text{day} = 2040$.

The adult dose level is adjusted by a factor of 1.7 to estimate child golfer exposure therefore $0.000612 \text{ mg a.i.}/\text{kg bw}/\text{day} * 1.7 = 0.00104 \text{ mg a.i.}/\text{kg bw}/\text{day}$.

MOE for child golfer is $1.25 \text{ mg a.i.}/\text{kg bw}/\text{day} \div 0.00104 = 1200$.

A MOE of 100 is adequate to protect golfers from dermal post-application exposures to treated golf course turf. Inhalation exposure is believed to be negligible. The proposed use does not exceed the Agency's level of concern as pertains to post-application exposures to adult and child golfers.

RESTRICTED ENTRY INTERVAL (REI)

Difenoconazole is classified in acute Toxicity Category III for acute dermal toxicity and primary eye irritation. It is classified in Toxicity Category IV for acute inhalation toxicity and primary skin irritation. It is negative as a dermal sensitizer. Therefore, the interim worker protection standard (WPS) REI of 12 hours is adequate to protect agricultural workers from most post-application exposures to difenoconazole.

ATTACHMENT

Summary of Toxicological Doses and Endpoints for Difenconazole for Use in Occupational Human-Health Risk Assessments.				
Exposure Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months)	Oral NOAEL = 1.25 mg/kg/day Dermal Absorption factor=15.3%	UF _A = 10X UF _H = 10X	Occupational LOC for MOE<100	Reproduction and fertility effects (rat; dietary) Offspring LOAEL = 12.5 mg/kg/day based on reduction in body-weight gain of F ₀ females prior to mating, gestation and lactation.
Dermal Long-Term (>6 months)	Oral NOAEL = 0.96 mg/kg/day Dermal Absorption factor=15.3%	UF _A = 10X UF _H = 10X	Occupational LOC for MOE<100	Combined chronic toxicity/carcinogenicity (rat; dietary) LOAEL = 24.1/32.8 mg/kg/day (M/F) based on cumulative decreases in body-weight gains.
Inhalation (Short- and Intermediate-term)	Oral NOAEL = 1.25 mg/kg/day 100% inhalation absorption assumed	UF _A = 10X UF _H = 10X	Occupational LOC for MOE<100	Reproduction and fertility effects (rat; dietary) Offspring LOAEL = 12.5 mg/kg/day based on reduction in body-weight gain of F ₀ females prior to mating, gestation and lactation.
Inhalation (Long-term)	Oral NOAEL = 0.96 mg/kg/day 100% inhalation absorption assumed	UF _A = 10X UF _H = 10X	Occupational LOC for MOE<100	Combined chronic toxicity/carcinogenicity (rat; dietary) LOAEL = 24.1/32.8 mg/kg/day (M/F) based on cumulative decreases in body-weight gains.
Cancer (oral, dermal, inhalation)	Difenconazole is classified as a Group C, possible human carcinogen with a non-linear (MOE) approach for human risk characterization (CPRC Document, 7/27/94, Memo, P. V. Shah dated March 3, 2007, HED Doc. No. 0054532).			

Abbreviations: UF = uncertainty factor, UF_A = extrapolation from animal to human (interspecies), UF_H = potential variation in sensitivity among members of the human population (intraspecies), UF_{FQPA} = FQPA Safety Factor, NOAEL = no-observed-adverse-effect level, LOAEL = lowest-observed-adverse-effect level, RfD = reference dose (a = acute, c = chronic), PAD = population-adjusted dose, MOE = margin of exposure, LOC = level of concern.

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13544

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